

REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 6-15 and 18-22 are pending in this application. Claim 1 has been amended by inserting the elements of previously pending claims 3, 5 and 15. Claim 15 as amended refers to a more specific type of administration, i.e. buccal administration. Claims 18 and 20 have had their dependencies changed to account for the other amendments to the claims. New claim 22 is directed to prednisolone as the active ingredient. Support for the elements of claims 15 and 22 can be found throughout the specification, e.g. see the Examples cited in the specification.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112.

II. THE OBJECTIONS TO THE CLAIMS HAVE BEEN OVERCOME

Claim 16 has been cancelled which renders this objection moot.

III. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

A. Claims 1, 3 and 5-21 were rejected as allegedly being obvious over Rupperecht et al. (U.S. Patent 6,780,504 – “Rupperecht”) in view of Becher (U.S. Patent 6,153,222) and Zerbe et al. (U.S. Patent 6,177,096 – “Zerbe”).

B. Claims 1, 3 and 5-21 were rejected as allegedly being obvious over Rupperecht et al. (U.S. Patent 6,780,504 – “Rupperecht”) in view of Becher (U.S. Patent 6,153,222) and Lydzinski et al. (U.S. Patent Application Publication 2003-0099692 – “Lydzinski”).

As both rejections rely on at least the combination of Rupperecht in view of Becher, the response to the above rejections are addressed collectively below.

1. Legal standards for determining obviousness

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc.* (KSR), 550 U.S. 398, 82 USPQ2d 1385 (2007), the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ

459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the art; and
- (D) Evaluating evidence of secondary considerations.

When ascertaining the differences between the prior art and the claims in issue, both the claimed invention and the prior art are considered as a whole.

Once the *Graham* factual inquiries are resolved, Office personnel must determine whether the claimed invention would have been obvious to one of ordinary skill in the art.

2. Differences between the claimed invention and the combination of Rupprecht, Becher, Zerbe and/or Lydzinski

Although there is some surface similarity between Rupprecht and the applicants' claimed dosage form, the combination of Rupprecht, Becher, Zerbe and/or Lydzinski still does not establish a *prima facie* case of obviousness. Moreover, the combination of references appears to be a rejection based on keyword association rather than the as a whole consideration of the respective references which is further explained in the discussion of the differences between the claimed invention and the cited references.

While the Office Action is somewhat correct in asserting a difference between Rupprecht and the presently claimed invention is the failure of Rupprecht to teach the use of glycerol in the active-ingredient containing layer of their film-dosage form, this is not precisely correct.

The applicants' claims specifically require that the glycerol is added and is present as a *plasticizer*¹ in the in-situ crosslinked hydrophilic polymers; the glycerol is not mere random post-polymerization additive to the polymer layer, but an integral part of the matrix formed by the in-situ crosslinking of the polymers, i.e. the mere presence of glycerol in the polymer product will not inherently give the characteristics of the applicants' claimed dosage form, the timing (in-situ) is also a critical aspect of the invention as is the identity of the compound used as a plasticizer (defined by the applicants as glycerol).

¹ "plasticizer" – an organic compound added to a high polymer both to facilitate processing and to increase the flexibility and toughness of the final product by internal modification (solvation) of the polymer molecule. (from pg. 1000 of *Hawley's Condensed Chemical Dictionary (Fifteenth Edition)*, ed. Richard J. Lewis, Wiley-Interscience (2007)).

Becher refers to the use of crosslinked polymers like carboxyvinyl copolymers (e.g. AquaKeep®) and/or crosslinked polyvinyl pyrrolidone (e.g. Kollidone® 90) as film formers in combination with glycerol as softener carboxyvinyl copolymers is a super absorbent polymer based on polyacrylate. Polyvinylpyrrolidone (PVP) is a water-soluble polymer made from the monomer N-vinylpyrrolidone (col. 2, lines 34-39, 56-63). Becher is characterized in the Office Action as merely lacking a teaching of the amount of glycerol based on the total amount of crosslinked hydrophilic polymer.

However, Becher does not teach the use of crosslinked *hydrophilic* polymers and as acknowledged in the Office Action, Becher only refers to glycerol as part of a “further substance” which includes the broad class of compounds such as fillers, active substances, foamers, film formers, flavoring agents, softeners and sweeteners, i.e. even if Becher had taught crosslinked hydrophilic polymers, Becher would not have directed one of ordinary skill in the art to a combination of glycerol as a plasticizer with *in situ crosslinked hydrophilic polymers*.

Zerbe refers to film forming *non-crosslinked* polymers comprising preferred water-soluble polymers selected from water-soluble cellulose derivates and polyacrylates, among others and one or more plasticizers or surfactants and one or more polyalcohols (col. 2, line 32-36). Glycerol is mentioned as an example of a polyalcohol (col. 3, line 10-15). The references teach 20 % of glycerol based on the total amount of the hydrophilic polymer, but not of the crosslinked hydrophilic polymer.

In contrast, the claim 1 as amended now refers to 30% - 60% glycerol content (which was originally part of dependent claim 2). which is not suggested by Zerbe and like Becher, only mentions glycerol in the context of broad classes of optional ingredients (“...the formulation may contain a combination of certain plasticizers or surfactants, colorants, sweetening agents, flavors, flavor enhancers, or other excipients commonly used to modify the taste of formulations intended for application to the oral cavity.”). Moreover, as noted above, the mere presence of glycerol will not produce the applicants claimed dosage form when modifying Rupprecht if the glycerol is not added properly. In the context of Zerbe, not only would the glycerol not be added properly, but one of ordinary skill in the art would be directed to use a non-claimed elements as the plasticizer.

Lydzinski refers to an oral film containing chemically modified *starch* which has been e.g. crosslinked. Plasticizers may be added to increase the apparent flexibility of the film particularly in an amount of about 15 % by weight of the starch component (page 2 [0026]). Potential plasticizers, among others include polyols. Glycerol is only mentioned as an example for polyesters (Glycerin Triacetat). Moreover, the claims as amended now refer to hydroxypropylmethylcellulose as the hydrophilic polymer.

None of Rupprecht, Becher, Zerbe and/or Lydzinski individually or collectively teaches using an active ingredient comprising layer based on in-situ crosslinked hydrophilic polymers using 30-60% glycerol as a plasticizer.

Plasticizers are normally employed in an amount of up to 20% by weight based on the amount of polymer. Even if one of ordinary skill in the art had been directed to use glycerol as a plasticizer during *in situ* polymerization, the state of the art would have directed the skill artisan away from using the amounts claimed by the application because when the percentage amounts of plasticizer are relatively high, phase separations may occur, e.g. due to crystallization, so that the films are no longer transparent and their physical properties such as the tear strength are adversely affected.

It is well known in the art that changing an element in polymer formulation can drastically affect the properties of the polymer formulation; not only was there no expectation of success for making the changes to Rupprecht suggested in the Office Action, the rejection presumes that one ordinary skill in the art considering the collective teachings of Becher, Zerbe, and Lydzinski would have only been directed to the (1) the teaching of the use of a plasticizer; (2) that glycerol would be that plasticizer to the exclusion of all the other elements which constitute the elements of Becher, Zerbe, and Lydzinski respective inventions.

As cited in the recent “Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex*” from the Federal Register (9/1/2010 – vol. 75, no. 169), “an obvious to try rationale may be proper when the possible options for solving a problem were known an finite. However, if the possible options were not either known or finite, then an obvious to try rationale cannot be used to support a conclusion of obviousness.” *Rolls-Royce PLC v. United Technologies Corp.*, 603 F.3d 1325 (Fed. Cir. 2010). The combination of Rupprecht, Becher, Zerbe and/or Lydzinski as applied in the Office Action tends to the infinite.

3. Optimization of ranges argument only works when the variable is first identified as a results-effective variable

The oft cited *In re Aller* (from MPEP 2144.05, section II.A.) makes yet another appearance in an Office Action, this time to assert that the amount of glycerol could have been optimized by one of ordinary skill in the art. As noted above, there is nothing within the combination of Rupperecht, Becher, Zerbe and Lydzinski which directs one of ordinary skill in the art to even use glycerol to address the deficiency of Rupperecht in the manner the applicants are using glycerol, i.e. as a plasticizer.

Moreover, it is well known that MPEP 2144.05 section II.B. (Optimization of Ranges) states that “A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).” There is nothing within the teachings of Rupperecht, Becher, Zerbe and Lydzinski which recognizes glycerol as a plasticizer as being a results effective variable.

4. Applicants have shown evidence of unexpected results

Consideration of obviousness also requires a consideration of any evidence of unexpected results. However, the evidence provided by the applicants was not addressed in the Office Action. While the applicants believe that the claimed invention is unobvious over the combination of Rupperecht, Becher, Zerbe and Lydzinski, given the positions staked out in the Office Action, the comparative examples were especially relevant as they compared the effect of having glycerol as a plasticizer vs. NOT having glycerol as a plasticizer.

Whereas the embodiments of the applicants claimed invention using glycerol as plasticizer show easy handleability and applicability to the human skin and mucous membrane, this was not true of comparative examples where no plasticizer was used (Comparative Example 1) or alternative plasticizers were used (polyethylene glycol (Comparative Example 2); sorbitol (Comparative Example 3); and triethyl citrate (Comparative Example 4)).

As such, the applicants claims are also unobvious because the applicants have surprisingly shown that the specific use of glycerol as a plasticizer allows one of ordinary skill in

the art to be able to use more plasticizer than was previously thought possible by those of skill in the art.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: /Howard C. Lee/
Marilyn M. Brogan Howard C. Lee
Reg. No. 31,223 Reg. No. 48,104
Telephone: (212) 588-0800
Facsimile: (212) 588-0500